REMARKS

Applicants acknowledge receipt of the Office Action mailed November 3, 2005. Claims 1-16 are pending. Claims 1 and 8 have been amended to recite specific NK-cell activating cytokines and NK-cell activating flavanoids. Support for the amendments to Claims 1 and 8 can be found throughout the specification and in the original claims as filed. Support can be found, for example, in paragraphs **[0010]** through **[0012]** and **[0035]** through **[0036]** of the specification. Claim 9 has been canceled. Claims 1-16 were rejected under 35 U.S.C. §112, first paragraph as failing to comply with the written description requirement. Claims 8, 9 and 11 were also rejected under 35 U.S.C. §103(a) as being obvious in view of the cited art. Claims 1-3, 6 and 7 were rejected under 35 U.S.C. §103(a) as being unpatentable over Hellstrand et al. (WO 91/04037) in view of the abstract of Oleksowicz et al. (Am. J. Ther. 1994 Aug; 1(2):107-115). Claims 1-8 and 11-16 are pending and presented for examination.

The pending claims particularly point out and distinctly claim the subject matter of the invention as required under 35 U.S.C. §112, second paragraph

Claim 9 was rejected under 35 U.S.C. §112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention. Claim 9 has been cancelled, thereby rendering the objection to this claim moot.

The specification provides adequate written description for the invention claimed in Claims 1-16 under 35 U.S.C. §112, ¶ 1

Claims 1-16 were rejected under 35 U.S.C. §112, first paragraph. 35 U.S.C. §112, first paragraph requires that the specification provide a written description of the invention. According to the PTO, the claims contain subject matter that was not described in the specification in such a way as to reasonably covey to one skilled in the relevant art that the inventors had possession of the claimed invention. Specifically, the PTO objected to the phrases "NK cell activating cytokine" and "NK cell activating flavanoid." Claims 1 and 8 have been amended to clarify specific NK cell activating cytokines and NK cell activating flavanoids. Applicants submit that the amendments to Claims 1 and 8 overcome the PTO's objection to the claims.

Claims 8, 9, and 11 are not obvious under 35 U.S.C. §103(a) over the abstract of Tatsuo (JP 59059628) or the abstract of Tatsuo (JP 59059627)

Claims 8, 9, and 11 were rejected under 35 U.S.C. §103(a) as being unpatentable over the abstract of Tatsuo (JP 59059628) or the abstract of Tatsuo (JP 59059627). Claim 8, as amended, is drawn to a method of inhibiting tumor growth in a subject suffering from neoplastic disease comprising administering an effective amount of an NK-cell activating flavonoid selected from the group consisting of flavone-8-acetic acid (FAA), xanthenone-4-acetic acid, analogs of FAA, and methyl-substituted derivatives of FAA and a hydrogen peroxide scavenger. Claim 9 has been cancelled. Claim 11 relates to the method of Claim 8, wherein the administration of the NK cell activating flavonoid and hydrogen peroxide scavenger is performed simultaneously. The abstract of Tatsuo (JP 59059628) (the '628 abstract) teaches an antitumor formulation comprising kaempferol and catalase. The abstract of Tatsuo (JP 59059627) (the '627 abstract) teaches an anti-tumor formulation comprising kaempferol and peroxidase. According to the PTO, even though the Japanese abstracts do not specifically state that kaempferol activates NK cells, the mere fact that kaempferol is a flavonoid compound and is combined with catalase or peroxidase to exert an anti-tumor effect is sufficient to establish *prima facie* obviousness. Applicants respectfully disagree.

To establish a *prima facie* case of obviousness a three-prong test must be met. First, there must be some suggestion or motivation, either in the references or in the knowledge generally available among those of ordinary skill in the art, to modify the reference. Second, there must be a reasonable expectation of success found in the prior art. Third, the prior art reference must teach or suggest all the claim limitations. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991). Applicants assert that the PTO has failed to establish a *prima facie* case of obviousness.

Claim 8, as amended, and the claims depending therefrom, relate to a method of inhibiting tumor growth comprising administering an effective amount of an NK-cell activating flavanoid selected from the group consisting of flavone-8-acetic acid (FAA), xanthenone-4-acetic acid (XAA), analogs of FAA, and methyl-substituted derivatives of FAA with a hydrogen peroxide scavenger. The '627 abstract discloses "[a]n antitumor formulation contains kaempferol, peroxidase, Fe, and Mn dissolved in either EtOH or olive oil." Similarly, the '628 abstract recites antitumor solutions containing kaempferol derivatives, catalase, Fe, and Mn in EtOH or olive oil. Notably, neither of these references describes or suggests modification of the reference teachings to

substitute other flavanoids for kaempferol to achieve the presently claimed inhibition of tumor growth.

Under 35 U.S.C. §103, prior art can be modified or combined to reject claims as *prima facie* obvious as long as there is a reasonable expectation of success. *In re Merck & Co., Inc.* 800 F.2d 1091 (Fed. Cir. 1986). Applicants submit that no such reasonable expectation of success exists in the present case. Here, Applicants have claimed a method of inhibiting tumor growth comprising the administration of specific NK-cell activating flavonoids with a hydrogen peroxide scavenger. The cited references relate to anti-tumor solutions comprising kaempferol and kaempferol derivatives, flavonoids not presently claimed. Kaempferol and the claimed flavonoids have different chemical structures and behave differently. Submitted herewith as Exhibit A, one journal article reports that the effect of various flavonoids on P-glycoprotein (P-gp) function in multidrug-resistant P-gp overexpressing KB-C2 cells differed. See Kitagawa et al. *Structure-activity relationships of the inhibitory effects of flavonoids on P-glycoprotein-mediated transport in KB-C2 cells*. Biol Pharm Bull. 28 (12): 2274-8 (2005) (attached as Exhibit A). Flavonoids such as kaempferol and quercetin behaved differently than a flavanone such as naringenin due to the differences in chemical structure. Similarly, in the Journal of Biomolecular Structure & Dynamics, scientists studies three different naturally occurring flavonoids and observed differences in DNA interaction between the various flavonoids. C.D. Kanakis et al., *DNA Interaction with Naturally Occurring Antioxidant Flavonoids Querectin, Kaempferol, and Delphinidin*, J of Biomol. Structure & Dynamics, 22 (6): 719-724 (2005) (a complimentary copy of which is submitted herewith as Exhibit B). Given the differences in chemical structure and activity of kaempferol and the claimed flavanoids, Applicants assert that there is no reasonable expectation of success in achieving the claimed invention.

Finally, Applicants submit that the claimed invention is not obvious in view of the '628 and '627 abstracts because neither reference teaches or suggests every claim limitation. As discussed above, Claim 8 (and therefore, the claims depending therefrom) has been amended to recite specific NK-cell activating flavanoids. These flavanoids are not described in either the '628 or '627 abstracts. Moreover, the abstracts are silent as to whether flavonoids other than kaempferol would have the same anti-tumor properties disclosed in the references. Because the abstracts do not disclose or suggest the use of NK-cell activating flavonoids selected from the group consisting of

flavone-8-acetic acid (FAA), xanthenone-4-acetic acid (XAA), analogs of FAA, and methyl-substituted derivatives of FAA, the references fail to establish a *prima facie* case of obviousness. Accordingly, Applicants respectfully request withdrawal of the rejection.

Claims 1-3, 6, and 7 are non-obvious under 35 U.S.C. §103(a) over Hellstrand et al. (WO 91/04037) in view of the abstract of Oleksowicz et al. (Am J Ther. 1994 Aug; 1(2):107-115).

Claim 1-3, 6, and 7 were rejected under 35 U.S.C. §103(a) over Hellstrand et al. (WO 91/04037) in view of the abstract of Oleksowicz et al. (Am J Ther. 1994 Aug; 1(2):107-115). According to the PTO, Hellstrand et al. teach a method of treating a neoplastic disease in a subject comprising the administration of histamine or other H2 receptor agonists in combination with the administration of IL-2. Oleksowicz et al. teach that IL-12 has been shown to enhance the lytic activity of non-specific NK/LAK cells and appears to be more efficient than IL-2 or IFNs in enhancing NK cytotoxicity. Thus, the PTO opines, it would have been *prima facie* obvious at the time the claimed invention was made to substitute IL-12 for IL-2 for the method of treating tumor growth taught by Hellstrand et al. Applicants respectfully disagree.

As set forth above, a *prima facie* case of obviousness is established when a three-prong test is met. First, there must be some suggestion or motivation, either in the references or in the knowledge generally available among those of ordinary skill in the art, to modify the reference. Second, there must be a reasonable expectation of success found in the prior art. Third, the prior art reference must teach or suggest all the claim limitations. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991). Applicants assert that the PTO has failed to establish a *prima facie* case of obviousness.

Applicants submit that it would not have been obvious to combine the reference teachings. This is because there must be some teaching, suggestion, or incentive to make the combination in the prior art. See, e.g. *In re Fine*, 5 U.S.P.Q. 1272 (Fed. Cir., 1988). No such teaching, suggestion, or incentive is provided by either of the cited references. Moreover, neither of the references, alone or in combination, suggests modification of the reference teachings to arrive at the presently claimed invention. Finally, the cited references provide no reasonable expectation of success in achieving the claimed invention. Accordingly, the present claims are non-obvious under 35 U.S.C. §103(a).

The teachings of the Hellstrand et al. reference are limited to the administration of IL-2 and histamine to stimulate NK cells. Hellstrand et al. fail to teach the administration of cytokines

other than IL-2 in combination with a compound that inhibits the production or release of hydrogen peroxide or scavenges hydrogen peroxide to stimulate NK cell activity. Because of this deficiency, the Hellstrand reference does not, either alone or in combination with Oleksowicz et al. reference, render the pending claims obvious. Oleksowicz et al. merely report that IL-12 enhances NK cytotoxicity and CTL responses. Oleksowicz et al. never mentions the potential role of IL-12 in NK-cell activation nor does it teach or suggest the synergistic effect in inhibiting tumor growth observed when an NK-cell activating cytokine other than IL-2 is administered with a compound that inhibits the production or release of hydrogen peroxide or scavenges hydrogen peroxide.

In fact, absent Applicants' present disclosure, there is no suggestion or motivation in the prior art to combine an NK cell activating cytokine or flavonoid other than IL-2 with a compound that inhibits the production or release of hydrogen peroxide or scavenges hydrogen peroxide. The cited art does not provide a suggestion of using a NK cell stimulator and a compound that inhibits the production of or scavenges hydrogen peroxide to stimulate NK cell cytotoxicity. There is no mention in the reference that NK cells activated by these various agents will be down-regulated in the presence of monocytes. Further, there is no suggestion that monocytes produce hydrogen peroxide as a mechanism for down regulating NK cells. Moreover, the reference is silent as to the potential for administering peroxide scavengers or inhibitors to potentiate the anti-tumor effects of NK cell activators in the presence of monocytes.

The cited references do not teach the administration of cytokines other than IL-2 with a compound that inhibits the production or release of hydrogen peroxide or scavenges hydrogen peroxide to stimulate NK cell activity. Additionally, the references neither describe nor suggest the greater than additive effects of the administration of an NK-cell activating compound with histamine or histamine-like compounds as is reported in the present application. Because of these deficiencies, the Hellstrand reference does not, either alone, or in combination with the Oleksowicz et al reference discussed above, render the pending claims obvious.

Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Kotzab*, 217 F.3d

1365 (Fed. Cir. 2000). Applicants submit that the PTO has pointed to no motivation to modify the reference teachings to arrive at the claimed method of inhibiting tumor growth by administering an NK cell activating cytokine or flavonoid with a compound effective to inhibit the production or release of hydrogen peroxide. Neither Hellstrand et al. nor Oleksowicz et al. describe any benefits the administration of a NK cell activating cytokine other than IL-2 or flavonoid with a compound effective to inhibit the production or release of hydrogen peroxide might evince in inhibiting tumor growth. Furthermore, neither reference describes, suggests, or appreciates the synergistic effect the co-administration of these compounds would have on inhibiting tumor growth.

Absent Applicants' present disclosure, there is no suggestion or motivation in the prior art to combine a NK-cell activating cytokine or flavonoid with a compound that inhibits the production or release of hydrogen peroxide or scavenges hydrogen peroxide. The mere fact that the reference teachings might be modified or combined does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. See *In re Mills*, 16 U.S.P.Q.2d 1430 (Fed. Cir. 1990); See, also M.P.E.P. §2143.01. In *In re Fine*, the Federal Circuit made clear that '[o]ne cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention." 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988). Instead, there must be some reason, suggestion, or motivation found in the cited references whereby a person of ordinary skill in the art would make the combination and that knowledge cannot come from the applicant's disclosed invention. See *In re Oetiker*, 24 U.S.P.Q.2d 1443 (Fed. Cir. 1992)(emphasis added). Absent impermissible hindsight, it would not have been obvious to administer a NK cell activating cytokine or flavonoid with histamine, other H_2 receptor agonists, or serotonin as is presently claimed.

Even if a *prima facie* showing of obviousness were established, the unexpected synergy that results from the combination of the NK cell activator and the hydrogen peroxide scavenger or inhibitor would clearly rebut such a showing. The data included in the specification demonstrate that the combination of an NK cell activating compound and a peroxide scavenger or inhibiting compound administered in the presence of monocytes not only prevents the inactivation of NK cells but also enhances NK cell cytotoxicity against tumor cells. These are unexpectedly superior results, since under similar circumstances, NK cell activators alone since

under similar circumstances, NK cell activators alone had no such beneficial effect (See, e.g. Examples 1 and 2 of the specification).

Applicants have demonstrated that the cited references fail to provide the necessary teaching, motivation, or suggestion to create a *prima facie* showing of obviousness. Moreover, even if there were a *prima facie* showing of obviousness, such a showing would be rebutted by the significant unexpected synergy provided by the claimed invention. Accordingly, Applicants respectfully request withdrawal of the Examiner's rejections under 35 U.S.C. §103.

CONCLUSION

For the foregoing reasons, it is respectfully submitted that the rejections set forth in the outstanding Office Action have been addressed and that the application is now in condition for allowance. Accordingly, Applicants request the expeditious allowance of the pending claims. The undersigned has made a good faith effort to respond to all of the rejections in the case and to place the claims in condition for immediate allowance. Nevertheless, if any undeveloped issues remain, or if any issues require clarification, the Examiner is respectfully requested to call the undersigned to discuss such issues.

Respectfully submitted,

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